The Examiner's objections and rejections are discussed and overcome as set forth below:

I. THE SECTION 112, SECOND PARAGRAPH REJECTION OF CLAIMS 1-2 AND 4-21

The Examiner rejected claims 1-2 and 4-21 under 35 USC Section 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as their invention.

The Examiner's rejections have been overcome as set forth below:

1. The Examiner's objection to the use of the term "cycloaliphatic" has been overcome by canceling claim 1 from the application without prejudice.

2. The Examiner's objection to the use of the term "aliphatic or cyloaliphatic amine group" has been overcome by canceling claim 1 from the application without prejudice.

3. The Examiner's objection to the use of the term "amine group" and "amino" has been overcome by canceling claim 1 from the application and by clarifying the use of the term in new claim 22.

4. The Examiner's rejection to the use of the term "group" in claim 2 has been overcome by canceling claim 2 from the application without prejudice.

5. The Examiner's rejection to duplicate claims has been overcome by canceling claim 3 from the application without prejudice.

6. The Examiner's rejection to the use of the term "Alzheimer's Disease" in claim 10 has been overcome by canceling the term from claim 10 without prejudice.

7. The Examiner's objection to the use of the allegedly redundant terms "blood vessel growth" and "cell growth" in claim 8. The objection has been overcome by canceling the term "cell growth" from claim 8 without prejudice.

8. The Examiner's objection to the use of the term "Sepsis" has been overcome by canceling the term from claim 12 without prejudice.

9-11. The Examiner's objections to the use the term "HIV", "HIV replication" and "TNF inhibition" in claim 12 has been overcome by canceling the objectionable terms from the claim without prejudice.

12. The Examiner's rejection to stray lines in the formula in claim 21 have been overcome by canceling claim 21 from the application and replacing it with identical claim 23 which includes the identical formula without the stray lines.

13. The Examiner's inquiry regarding the term "neurosecretion" has been overcome by amending claim 8 without prejudice to encompass methods for regulating A_{2A} antagonist mediated neurotransmitter secretion. This amendment finds support at page 5, lines 19-24 of the specification.

II. THE SECTION 112, FIRST PARAGRAPH REJECTIONS

The Examiner's rejection of claim 11 under 35 U.S.C. section 112, first paragraph has been overcome by canceling claim 11 from the application without prejudice.

The Examiner's rejection of claim 10 under 35 U.S.C. section 112, first paragraph has been overcome by amending the claims to encompass methods for treating depression only as suggested by the Examiner.

The Examiner's rejection of claim 12 under 35 U.S.C. section 112, first paragraph has been overcome by amending claim 12 to remove the allegedly overly broad diseases from the claim without prejudice.

The Examiner's rejection of claim 8 (identified as claim 12 in the Official Action) under 35

U.S.C. section 112, first paragraph has been overcome by canceling the allegedly overly broad indications from the method claim without prejudice.

The Examiner's rejection of claim 20 under 35 U.S.C. section 112, first paragraph has been rendered moot by canceling claim 20 from the application without prejudice.

III. THE OBVIOUSNESS REJECTIONS

The Examiner rejected claims 1-2, 4-6, and 11-19 under 35 USC §103(a) as being unpatentable over EP 386683. The Examiner also rejected claims 1-2 and 4 as being unpatentable over Bonte, U.S. Patent No. 5,470,579. Both of these obviousness rejections are traversed as set forth below.

A. EP 386683

Claims 1-2 have been canceled from the application without prejudice and replaced with new composition claim 22. Claims 5-10, 12 and 19 have also been amended to convert them into independent claims that recite methods for using the compounds recited in new claim 22 for treating specific indications.

EP 386683 does not render pending application claims 4-6, 11-19 and new claim 22 obvious because the claimed compositions are unexpectedly more potent than compositions of the prior art. As Dr. Wells, one of the Applicant's explains in his Declaration – which is attached hereto – compounds of EP 386683 with a propyl at the 3-position are not homologues of compounds of the present invention with iosbutyl at the 3-position. Dr. Wells compared several substitutions at the 3-position and found that 3-isobutyl xanthine is 4.5-fold more potent in inhibiting A_{2B} receptor mediated effects compared to 3-propyl xanthine. The compounds of claim 22, therefore, have unexpectedly improved potencies in comparison to compounds of the prior art thereby rendering

the claim patentable.

B. Bonte U.S. Patent No. 5,470,579

The Examiner rejected claims 1-2 and 4 as being obvious over U.S. Patent No. 5,470,579 to Bonte et al.

The Applicants have overcome this rejection, in part, by limiting the method of claim 4 to the compound set forth in new claim 23.

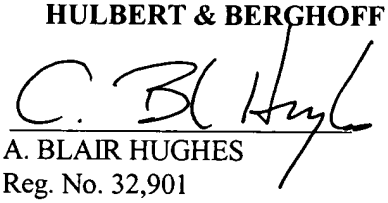
Claims 1-2 have been cancelled from the application and rewritten in independent and amended form in new claim 22. New claim 22 is believed to be patentable over Bonte et al. the claimed compounds are believed to have superior activity in comparison to the Bonte et al. compounds.

In view of the amendments and arguments presented above, it is believed that all pending claims 4-10, 12-19 and 22-23 of this application are allowable and that all rejections and objections should be withdrawn. Favorable reconsideration and allowance of the application claims is, therefore, courteously solicited.

Respectfully submitted,

McDONNELL BOEHNEN HULBERT & BERGHOFF

Dated: March 12, 2002

By: 

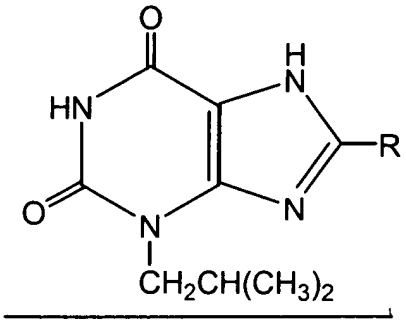
A. BLAIR HUGHES
Reg. No. 32,901
(312) 913-2123

APPENDIX A

Marked Up Claims Pursuant To 37 CFR 1.121

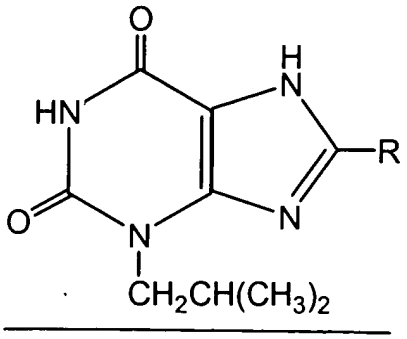
4. (Once amended) A pharmaceutical composition comprising a compound of [formula (I)]claim 23 and a pharmaceutically acceptable carrier.

5. (Once amended) A method of antagonizing A_{2B} receptors comprising administering to a mammal in need thereof an effective amount of a compound of the following formula:



wherein R is selected from C_1 to C_6 alkyl amine, C_1 to C_6 dialkyl amine, unsubstituted piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof [of claim 1].

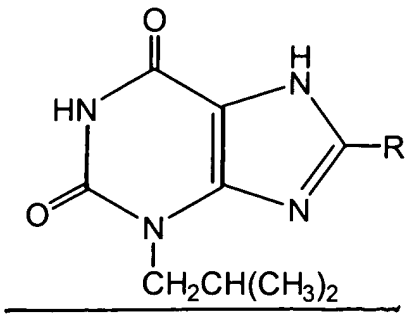
6. (Once amended) A method of treating asthma comprising administering to a mammal in need thereof an effective amount of a compound of the following formula:



wherein R is selected from C_1 to C_6 alkyl amine, C_1 to C_6 dialkyl amine, unsubstituted piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof [claim 1].

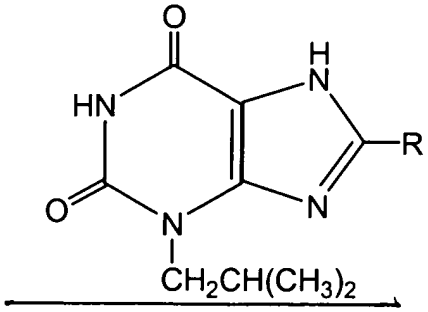
7. (Once amended) A method of treating diarrhea comprising administering to a mammal

in need thereof an effective amount of a compound of the following formula:



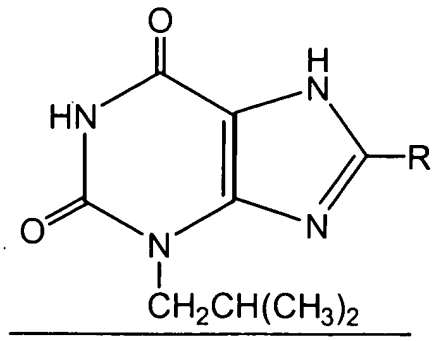
wherein R is selected from C_1 to C_6 alkyl amine, C_1 to C_6 dialkyl amine, unsubstituted piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof[claim 1].

8. (Once amended) A method of regulating at least one of smooth muscle tone, [cell growth,] blood vessel growth, [intestinal function,] and [neurosecretion] A_{2A} antagonist mediated neurotransmitter secretion comprising administering to a mammal in need thereof an effective amount of a compound of the following formula:



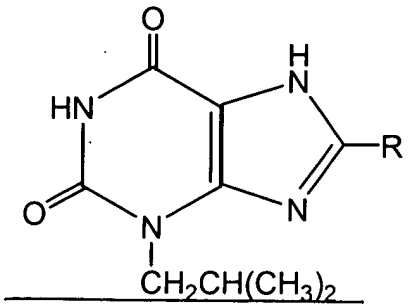
wherein R is selected from C_1 to C_6 alkyl amine, C_1 to C_6 dialkyl amine, unsubstituted piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof[claim 1].

9. Once amended) A method of treating inflammatory gastrointestinal tract disorders comprising administering to a mammal in need thereof an effective amount of a compound of the following formula:



wherein R is selected from C_1 to C_6 alkyl amine, C_1 to C_6 dialkyl amine, unsubstituted piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof[claim 1].

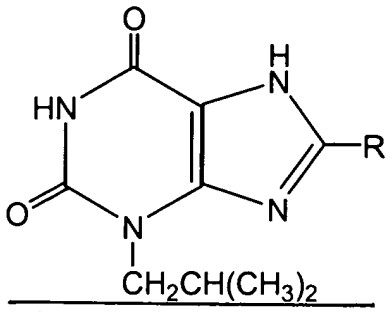
10. (Once amended) A method of treating [Alzheimer's disease, Parkinson's disease, dementia,] depression[, or traumatic brain injury] comprising administering to a mammal in need thereof an effective amount of a compound of the following formula:



wherein R is selected from C_1 to C_6 alkyl amine, C_1 to C_6 dialkyl amine, unsubstituted piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof[claim 1].

12. (Once amended) A method treating a disease selected from the group consisting of: arthritis, asthma, multiple sclerosis,[sepsis,] septic shock, endotoxic shock, gram negative shock, toxic shock, hemorrhagic shock, adult respiratory distress syndrome, [TNF-enhanced HIV replication, TNF inhibition of AZT and DDI activity,] organ transplant rejection, cachexia secondary to cancer, [HIV], osteoporosis, infertility from endometriosis, [cerebral malaria,] bacterial meningitis, adverse effects from amphotericin B treatment, adverse effects from interleukin-2 treatment, adverse effects from OKT3 treatment, or adverse effects from GM-CSF

treatment comprising administering to a mammal in need thereof, an effective amount of a compound of the following formula:



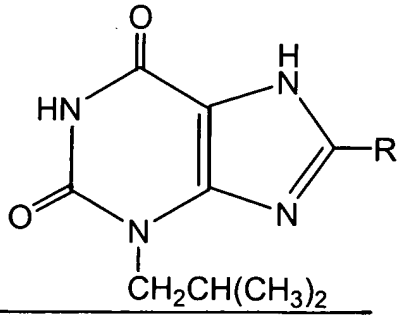
wherein R is selected from C_1 to C_6 alkyl amine, C_1 to C_6 dialkyl amine, unsubstituted piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof[claim 1].

13. (Once amended) The method of claims 5 or 6 or 8 or 9 or 10 or 12, wherein said compound is incorporated with inert carriers into a tablet and administered orally.

14. (Once amended) The method of claims 5 or 6 or 8 or 9 or 10 or 12, wherein said compound is incorporated with a propellant and a solvent and administered by inhalation of mist.

15. (Once amended) The method of claims 5 or 6 or 8 or 9 or 10 or 12, wherein said compound is incorporated with a pharmaceutically acceptable carrier and injected into said mammal.

19. (Once amended) A method of modulating human mast cell function comprising administering to a patient in need thereof an effective amount of a compound of the following formula:



wherein R is selected from C_1 to C_6 alkyl amine, C_1 to C_6 dialkyl amine, unsubstituted

piperidino, piperazino, pyrrolidino, pyrrolino, morpholino, an amino cyclohexyl derivative or a pharmaceutically acceptable salt thereof [claim 1].

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. MBHB00-618-A)

In the Application of:

Italo O. Biaggioni et al.

Serial No.: 09/648,775

Filed: August 28, 2000

Title: Selective Antagonits of A2B Adenosine Receptors

Art Unit: 1624

Examiner: M. Berch

Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION OF DR. JACK N. WELLS
(PURSUANT TO 37 C.F.R SECTION 1.132)

I Jack N. Wells, residing at 3604 Saratoga Drive, Nashville, TN, 37205, do hereby declare:

1. I am a named inventor of this United States Letters Patent Application Serial No. 09/648,775, filed on August 28, 2000.

2. I hold an Ph.D degree in Pharmaceutical Chemistry from The University of Michigan.

3. I am currently, Professor of Pharmacology at Vanderbilt University School of Medicine. I have been actively pursuing the design of drugs and Pharmacological research at Vanderbilt University school of Medicine for twenty-nine years. I have been actively engaged in the synthesis of xanthine-based molecules, first as inhibitors of cyclic nucleotide phosphodiesterases and as antagonists of adenosine receptors for the last fifteen-years. I have authored over seventy-five articles in peer-reviewed scientific journals. Prior to joining the Faculty at Vanderbilt, I was on the faculty of the Department of Medicinal Chemistry, Purdue University for nine-years.

4. I have reviewed and understand EP 0386683. In addition, I have reviewed the Examiner's Official Action dated September 24, 2001 in this case.

5. I understand that EP 386683 discloses xanthine derivatives that include compounds with a propyl substituent at the 3-position of instead of the isobutyl substituent of the claimed compounds. These are, however, not homologues. I have compared several substitutions in this position and found that 3-isobutylxanthine is 4.5-fold more potent in inhibiting A_{2B} receptor mediated effects compared to 3-propylxanthine. (See "compound 22", 3-isobutylxanthine, and "compound 25", 3-propylxanthine, in Table 1D of Feoktistov et al., Inhibition of human mast cell activation with the novel selective A2B receptor antagonist 3-isobutyl-8-pyrrolidinoxanthine (IPDX). Biochemical Pharmacology 2001;62:1163-1173 attached to my Declaration as Appendix A). Furthermore, EP 386683 discloses compounds having bronchodilating activity (which is likely an effect mediated by blocking A1 receptors) that are 1.9-2.3-fold more potent than theophylline. The compound of formula II is at least 10-fold more potent than theophylline in inhibiting A_{2B}-mediated effects. The compounds claimed under this patent application, therefore, have unexpectedly improved potencies in comparison to compounds of the prior art.

I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that theses statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed: Jack N. Wells
Dr. Jack N. Wells

Date: 3-11-02